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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,433	02/24/2004	Avi Ashkenazi	P1216R1C1D3	1225

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/785,433	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/04 & 4/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Attachment I*.

DETAILED ACTION

1. Claims 49-59 are pending and under examination in the instant application.

2. Applicant's IDS, filed 4/7/04 and 4/18/05, is acknowledged. Only the references initiated, IDS file 6/7/04, were found in the parent applications 09/953,499 and 09/254,465. The BLAST results provided as reference Nos. 15-17 are not appropriate for an IDS. BLAST alignments should be appended as part of each individual sequence reference, which must include the Accession No., Database and earliest available date of the reference sequence in order to be appropriate for inclusion in the IDS. Further reference C1, filed 4/18/05, was crossed out because it is a duplicate of reference 210 filed on 6/7/04.

3. The specification on page 49, lines 36-40, discloses that clone DNA40628 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 52-54 (FIG. 5; SEQ ID NO: 11). The sequence listing SEQ ID NO:11 does not correspond with the translation initiation site at nucleotide positions 52-54. Clarification is required.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification contains the nucleic acid sequence of 1,842 bp on Fig.5, which is not present in sequence listing. While the sequence identifier indicates that said nucleic acid is SEQ ID NO:11, the sequence listing indicates that SEQ ID NO: 11 is 2181 nucleotide sequence.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "at least 99% amino acid sequence identity" claimed in claim 53, line 1represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 2/24/04 dose not point to the specification for support for the newly added limitations "at least 99% amino acid sequence identity" as claimed in claim 53. However,

the specification does not provide a clear support for such limitation. The instant claims now recite a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

7. Claims 49-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the pRK5-based plasmid DNA40628-1216 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the plasmid, may satisfy first paragraph. See 37 CFR 1.801-1.809.

The amendment to the specification on page 68, filed 2/24/04, to assure that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, is acknowledged. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at lest 30 years *and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.* See 37 C.F.R. 1.806.

8. Claims 49-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide molecule having the amino acid sequence of the polypeptide of SEQ ID NO: 1 with or without its associated signal peptide for the inhibition of VEGF stimulated proliferation of endothelial cells, does not reasonably provide enablement for any isolated polypeptide molecule having "at least 80%, 85%, 90, 95%, 99% amino acid sequence identity" to (a) the amino acid of the polypeptide of SEQ ID NO: 1 (b) the amino acid sequence of the polypeptide of SEQ ID NO: 1, lacking its associated signal peptide; or (c) the amino acid of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209432 in claims 49-53. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The claims are directed to isolated polypeptide having at least 80%, 85%, 90%, 95%, or 99% sequence identity to SEQ ID NO: 1 with or without it single sequence.

The specification discloses that PRO301 A33 antigen (see Figure 1, and page 1, lines 36-37). Further the specification, on page 7, lines 39-40 discloses that the PRO301 polypeptide is 299 amino acids long, having signal sequence at residue 1-27, and extracellular domain at residue 28-235, Ig superfamily homology at residue 94-235, a potential transmembrane domain at residue 236-258, and an intracellular domain at about residue 259-299. The specification on page 53, under example 4, discloses the use of the protein of SEQ ID NO:1 in the inhibition of VEGF stimulated proliferation of endothelial cells growth.

The claims encompass an unreasonable number of inoperative polypeptide, which the skilled artisan would not know how to use. There are no working examples of amino acids less than 100% identical to SEQ ID NO:1. The specification fails to provide guidance for using polypeptides related to (i.e. at least 80-99% identity) but not identical to SEQ ID NO:1 that share the ability to inhibit endothelial cell growth of the encoded polypeptide of SEQ ID NO:1, other than the amino acid of SEQ ID NO:1.

The art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the instantly recited nucleic acid sequence is unpredictable, as is the identity of which subsequences would hybridize to SEQ ID NO:11 encoding SEQ ID NO: 1 with or without signal sequence; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

9. Claims 49-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an isolated polypeptide molecule having the amino acid sequence of the polypeptide of SEQ ID NO: 1 with or without its associated signal peptide for the inhibition of VEGF stimulated proliferation of endothelial cells.

Applicant is not in possession of any isolated polypeptide molecule having "at least 80%, 85%, 90, 95%, 99% amino acid sequence identity" to (a) the amino acid of the polypeptide of SEQ ID NO: 1 (b) the amino acid sequence of the polypeptide of SEQ ID NO: 1, lacking its associated signal peptide; or (c) the amino acid of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209432 in claims 49-53.

Applicant has disclosed only amino acid of SEQ ID NO: 1 with or with out signal sequence; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The priority is set at 11/20/1998 for the claimed nucleic acid because the utility for the encoded protein is active in the inhibition of VEGF stimulated proliferation of endothelial cells. The earliest disclosure of this result that can be confirmed by the Examiner is in the PCT/US98/24855. Accordingly, the rejections below base on the Examiner's determination of the priority date.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 49-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Naik *et al* (Biochem. J. 310:155-162, 1995), as is evidenced by Sobocka *et al.*

Naik *et al* teach a novel platelet receptor, F11antigen. Also, Naik *et al* teach that the N-terminal 26 amino acid sequences of the F11 antigen, which has 32 and 35 kDa protein, were identical and contained a single unblocked serine in the N-terminal position. Further, when digested with N-glycanase, the 32 and 35 kDa proteins were converted into a single ~29 kDa protein, indicating that these two proteins are derived from the same core protein but differ in their degree of glycosylation. Naik *et al* teach that the internal amino acid sequence analysis of the F11 antigen provided information concerning 68 amino acids and suggested two consensus phosphorylation sites for protein kinase C (PKC) (see abstract, page 159, 2nd col., 2nd paragraph, and page 160, 2nd col., 1st paragraph in particular). While Naik *et al* is silence with respect to SEQ ID NO: 1, referenced F11 antigen is the claimed SEQ ID NO: 1 as is evidenced by Sobocka *et al* that the reported sequence of human homologue of JAM (claimed SEQ ID NO: 1, see attached sequence alignment in particular) by Martin-Padura et al and Ozaki et al, is identical to the sequence of the human platelet F11R (see page 2607, 1st col., end of the 1st paragraph). Applicant's disclosure of SEQ ID NO:1 is mainly further characterization of otherwise old product.

The reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naik *et al* (Biochem. J. 310:155-162, 1995*)*, as is evidenced by Sobocka *et al* in view of U.S. Patent No. 6,472,520.

The teachings of Naik *et al* reference and Sobocka *et al evidentiary* reference have been discussed, supra.

The claimed invention differs from Naik et al reference teachings only by the recitation of a chimeric polypeptide comprising a polypeptide molecule fused to a heterologous polypeptide in claim 58, wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin in claim 59.

The `520 patent teaches a polypeptide can comprise a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His or hemagglutinin), or to enhance binding of the polypeptide to a solid support. Fusion proteins capped with such peptides may also be resistant to intracellular degradation in E. coli. Protein fusions, for example, polypeptides conjugated to an immunoglobulin Fc region or a leucine zipper domain (Column 45, lines 43-55 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to fuse the soluble polypeptide taught by Naik et al with peptide linker, an Fc or a leucine zipper domain as taught by the `520 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such fusion polypeptide are use for ease of synthesis, purification or identification of the polypeptide, or to enhance binding of the polypeptide to a solid support as taught by the `520 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 13, 2006

Maher Haddad

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